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COMMENTARY

Genomic Catastrophe and Neoplastic Transformation

William B. Coleman

From the Department of Pathology and Laboratory Medicine, Curriculum in Toxicology, UNC Program in Translational Medicine, UNC Lineberger Comprehensive Cancer Center, University of North Carolina School of Medicine, Chapel Hill, North Carolina

Cell Fusion and Cancer

Theodor Boveri published his groundbreaking work approximately 100 years ago suggesting that neoplastic transformation and cancer induction was "…a consequence of a certain abnormal chromosome constitution…"[1,p21] This observation was particularly insightful given that it came decades before the general acceptance of DNA as the genetic material in animal cells, and well before the molecular underpinnings of cancer were defined.

We have witnessed a molecular revolution in biology and have gained great understanding of the genes, pathways, and molecular mechanisms of cancer development and progression.[2] Despite our increased understanding of the hallmark features of cancer[3] and the governing mechanisms, we lack fundamental understanding of how cancer develops (spontaneously) from normal cells in the absence of inherited gene defects, infection by oncogenic viruses, or exposure to environmental carcinogens. The study by Zhou et al[4] used an innovative experimental design that enabled examination of oncogenic molecular events occurring early after fusion of normal (nonneoplastic) rat intestinal crypt epithelial (IEC-6) cells. The objective of this study was to determine whether a cell fusion event involving normal cells will precipitate molecular alterations that drive neoplastic transformation and tumorigenesis. Cell fusion has been suggested as a possible initiating event in cancer development based on several observations: i) cell fusion events can be detected in existing cancers,[5] ii) cell fusion is associated with genomic instability, which could drive neoplastic transformation,[6] and iii) cell fusion may account for neoplastic transformation among nonproliferative differentiated cell types.[7]

Experimental Model of Cell Fusion

Zhou et al[4] used rat IEC-6 cells[8] which have a stable diploid karyotype, lack cellular characteristics of neoplastically-transformed cells *in vitro*, and fail to form tumors in animals after repeated passaging in cell culture. IEC-6 cells were fluorescently labeled using either green (CSFE) or red (SNARF-1) dyes, mixed, cell fusion was mediated with 50% polyethylene glycol (PEG), and the resulting cell population was subjected to fluorescence-activated cell sorting (FACS) to identify fused and non-fused cells. Fused cells were larger in size and exhibited dual fluorescent signal, whereas non-fused cells were of normal size and displayed only one fluorescent marker.[4] Fused cells were sorted and clonal populations were established and subsequently characterized for growth properties *in vitro*, markers of DNA damage, and tumorigenic potential *in vivo*.[4]

Cell Fusion Engenders Genomic Instability and DNA Damage

Fusion-derived IEC-6 cell clones were successfully established from 19% of FACS-sorted cells,[4] suggesting that a subset of cell fusion events result in clones that can proliferate and expand. Among the fusion-derived IEC-6 cell clones examined, 41% were aneuploid and 56% were near-diploid, whereas 86% of non-fused cell clones were diploid.[4] This suggests that cell fusion engenders genomic instability.

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Address correspondence to William B. Coleman, Ph.D., Department of Pathology and Laboratory Medicine, CB#7525, Room 515 Brinkhous-Bullitt Bldg., University of North Carolina School of Medicine, Chapel Hill, NC 27599. E-mail: wbcolemn@med.unc.edu.

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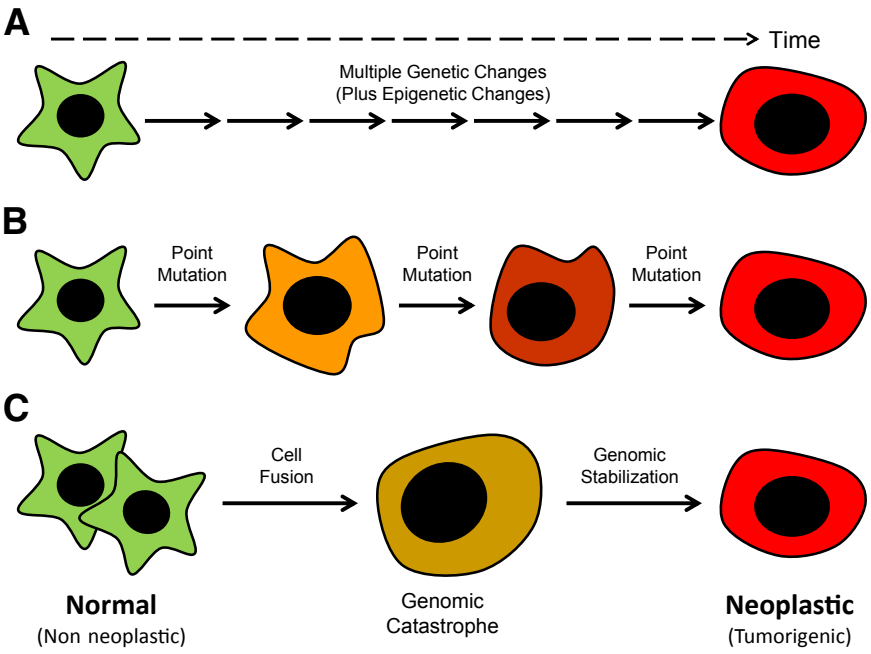

Figure 1 Molecular pathways to neoplastic transformation and tumorigenesis. **A:** Carcinogenesis is accepted to be a multistep process where successive molecular alterations occur over time, and each one produces some growth advantage that enables emergence of a new dominant clonal population. With accumulation of the critical number (and nature) of molecular events, neoplastic transformation occurs and a clonal population with tumorigenic potential is established. **B:** During neoplastic transformation, critical molecular targets are activated or inactivated through genetic or epigenetic mechanisms. Point mutations can activate or inactivate critical genes leading to neoplastic transformation. Alternatively, chromosomal alterations or epigenetic changes (like DNA hypermethylation) may contribute (along with point mutations) to neoplastic transformation. The critical number of events has not been established. **C:** Genomic catastrophe is a mechanism for the concurrent generation of the critical number (and nature) of molecular events over a very short period of time resulting in neoplastic transformation and tumorigenic potential in the incipient cell population. Genomic catastrophe may require a precipitating event in which an unstable tetraploid intermediate is established secondary to cell fusion or some other cellular event.

Furthermore, examination of the ploidy state of fusion-derived IEC-6 cell clones over time in culture revealed karyotypic instability where near-tetraploid clones became near-diploid after time in cell culture.[4] Fusion-derived IEC-6 cell clones were also heterogeneous with respect to ploidy; near-diploid clones with a modal chromosome number of 42 exhibited a wide range of chromosome numbers indicating the presence of significant subpopulations of aneuploid cells within the cell population.[4] These observations combine to suggest that early after a cell fusion event, the genomes of fusion-derived clones exhibit instability that manifests as changes in ploidy, with generation of aneuploid clones, near-diploid clones that likely have aberrant karyotypes despite a near-normal chromosome number, and near-diploid clones that contain significant subpopulations of aneuploid cells. In addition to chromosomal instability, fusion-derived IEC-6 cell clones exhibited DNA damage in the form of double-strand breaks; 35% to 42% of cells from fusion-derived clones exhibited evidence of double-strand breaks compared to only 4% to 9% of nonfused clones.[4] Despite DNA damage in fusion-derived IEC-6 cell clones, activated caspase 3 was rarely detected, indicating that DNA damage does not lead to apoptosis in these cells.

Cell Fusion Leads to Neoplastic Transformation

The results indicate that chromosomal instability (with changes in ploidy) and DNA damage (double-strand breaks) rapidly follow a cell fusion event. Zhou et al[4] examined cellular growth characteristics *in vitro* for evidence of neoplastic changes in fusion-derived IEC-6 cell clones. A subset of fusion-derived clones (32%) lost contact-inhibition after 12 passages *in vitro*, whereas 29% of fusion-derived clones acquired anchorage-independent growth capability.[4] In contrast, 3% of non-fused clones lost contact inhibition, and 2% acquired anchorage-independent growth capability over the same period of time in culture.[4] These results suggest that fusion-derived IEC-6 cell clones display cellular growth characteristics consistent with neoplastic transformation. However, in many cases, *in vitro* cellular characteristics do not accurately predict tumorigenic potential *in vivo*. Hence, to definitively test whether a cell fusion event can lead to neoplastic transformation, Zhou et al[4] transplanted cells from a pool of fusion-derived IEC-6 cells into immunodeficient mice and tumor formation was monitored over 12 weeks. Tumors were produced in 11 of 18 host mice (61%), whereas no tumors were produced from the transplantation of the parental IEC-6 cells or non-fused clones.[4] In addition, fusion-derived IEC-6 cell clones ($n = 9$ tested) that lost contact inhibition and acquired anchorage-independent growth potential formed tumors on transplantation with great efficiency.[4] In contrast, fusion-derived IEC-6 cell clones that did not demonstrate cellular growth characteristics associated with neoplastic transformation *in vitro* failed to form tumors on transplantation into immunodeficient mice ($n = 2$ clones tested).[4] Of note, the karyotype of tumorigenic fusion-derived IEC-6 cell clones did not change during the process of tumorigenesis *in vivo*, and the tumorigenic properties of fusion-derived clones (the percentage of hosts developing tumors and tumor growth rate) were stable, suggesting that these properties were established at the time of cell fusion or rapidly following that event.[4] These results combine to indicate that i) cell fusion can lead to neoplastic transformation

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